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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/580,589	ROGUEDA, PHILIPPE	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *7 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/25/06* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 are pending. Claims 7 and 10 are withdrawn as being drawn to non-elected subject matter, per the restriction requirement set forth below. **Claims 1-6 and 8-9 are under consideration in the instant office action**.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) claims, drawn to an HFA drug formulation comprising a partially or fully acylated alpha, beta, or gamma cyclodextrin.

Group II, claim(s) 10, drawn to a method of treating a respiratory disease.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of group I, namely a drug formulation comprising a cyclodextrin and a HFA is already known in the prior art, as evidenced by Williams, R.O. and Liu, J., "Influence of formulation technique for hydroxypropyl-beta-cyclodextrin on the stability of aspirin in HFA 134a," *European Journal of Pharmaceutics and Biopharmaceutics*, **1999**, *47*, pp 145-152 (especially section 2.2.4 on page 147) and Uekema et al. ("Cyclodextrin Drug Carrier Systems," *Chem. Rev.* **1998**, *98*, pp 2045, 2048 (Table 2); and 2063).

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

(a) Drug (Groups I and II)

(b) Respiratory disease being treated (Group II only)

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed above in the following manner:

Claims 1-10 correspond to species (a) and claim 10 corresponds to species (b)

The following claim(s) are generic: claims 1-10 are generic for the drug and claim 10 is generic for the respiratory disease.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: (a) the special technical feature of a drug is its active core structure, because drugs have divergent chemical structures each drug has a different special technical feature; and (b) each respiratory disease is characterized by a different etiology, and the diseases encompassed by Applicants' claim 10 include diseases exhibiting unrelated etiological origins and requiring different treatment regimens. Thus, each respiratory disease treated represents a different special technical feature.

During a telephone conversation with Mr. John Kendall, Esq. on September 23, 2009 at ~2:48 pm EST a provisional election was made without traverse to prosecute the invention of

Group I, claims 1-9. Affirmation of this election must be made by applicant in replying to this Office action. **Claims 7 and 10 are withdrawn** from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Drawings

The drawings are objected to because Figure 3 is illegible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for

consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The specification is objected to because it is missing a heading entitled, "Brief Description of the Several Views of the Drawing(s)".

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.

(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for solvates of budesonide. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Determination of Claim Scope

Claim 6 of the instant application claims a pharmaceutical composition comprising (i) any HFA (hydrofluoroalkane), (ii) a drug selected from a Markush group consisting of the species recited in claim 6, including the elected drug, budesonide, and (iii) a partially or fully acylated alpha-, beta-, or gamma-cyclodextrin, wherein included in the scope of the drug are ***solvates*** thereof. The term solvates is inclusive of hydrates as well.

Review of Applicants' Disclosure

The instant specification does not disclose, to which solvates of budesonide Applicants are referring. Applicants' specification does not disclose how to make any particular solvate of budesonide, nor do Applicants depict chemical structures of budesonide as any particular solvate in their disclosure.

Possession Based on Ordinary Skilled Artisan's Determination/ State of the Prior Art

It is generally accepted in the art that the formation of a particular solvate, polymorph, or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, 1-26, especially pp 1, 11-12, and 18), therefore, the generic reference to a solvate of budesonide in the instant specification does not provide adequate written support for claims drawn to any solvate this compound. Braga et al. (*Chem. Commun*., "Making Crystals from Crystals: a green route to crystal engineering and polymorphism," **2005**, pp 3635-3645) states on page 3640, "One can say that if the formation of polymorphs is a nuisance for crystal engineers, solvate formation can be a nightmare, because it is extremely difficult to predict whether a new species may crystallize[s] from solution with one or more molecules of solvent." The state of the art is such that in this century **there should not be any doubt as to the chemical identity of a material** (Seddon, K.R., "Pseudopolymorph: a polemic," *Crystal Growth & Design*, **2004**, *4(6)*, pp 1087, web release date October 19, 2004). A search of the prior art did not uncover any specific solvates of budesonide.

An ordinary skilled artisan would conclude that Applicants were not in possession of any particular solvate of budesonide of the claimed composition. Furthermore, because Applicant's generic reference to solvates of budesonide does not permit the ordinary skilled artisan to clearly

envisage which specific solvates of budesonide were in Applicant's possession, the only reasonable conclusion said artisan would make was that Applicant was not in possession of solvates of budesonide and had not reduced to practice the preparation, isolation, and characterization of said solvates.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising budesonide in the form of a neutral compound and/or pharmaceutically acceptable acid addition salts thereof, does not reasonably provide enablement for compositions comprising solvates of budesonide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicant's claim is broad with regards to the subgenera of solvates and physiologically acceptable acid addition salts of budesonide.

Nature of the invention/State of the Prior Art

Claim 6 of the instant application claims a pharmaceutical composition comprising [(i) any HFA (hydrofluoroalkane), (ii) a drug selected from a Markush group consisting of the species recited in claim 6, including the elected drug, budesonide, and (iii) a partially or fully acylated alpha-, beta-, or gamma-cyclodextrin, wherein included in the scope of the drug are ***solvates*** thereof is representative of the nature of Applicants' invention. It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 11 and 18). Braga et al. (*Chem. Commun.*, "Making Crystals from Crystals: a green route to crystal engineering and polymorphism," **2005**, pp 3635-3645) states on page 3640, "One can say that **if the formation of polymorphs is a nuisance for crystal engineers, solvate formation *can be a nightmare***, because it is extremely difficult to predict whether a new species may crystallize[s] from solution with one or more molecules of solvent." The state of the art is such that in this century **there should not be any doubt as to the chemical identity of a materia**l (Seddon, K.R., "Pseudopolymorph: a polemic," *Crystal Growth & Design*, **2004**, *4(6)*, pp 1087, web release date October 19, 2004). A search of the prior art did

not uncover any specific solvates of budesonide.

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970). The art is especially unpredictable with regards to the existence and formation of particular polymorphs and solvates of chemical compounds, as set forth above by the teachings of Vippagunta et al. and Braga.

Guidance/Working Examples

Applicants provide no guidance or working examples about the preparation of any solvate budesonide

The prediction and preparation of a particular solvate (i.e. a polymorph, wherein a molecule of solvent is part of the crystalline unit cell) is highly unpredictable. Because the prior art and Applicant's specification are silent as to the preparation of any specific solvate of budesonide, it would be an undue burden for an ordinary skilled artisan to ascertain how to make and isolate any possible unknown solvates of budesonide that may or may not exist. The ordinary skilled artisan would be forced to commence burdensome experimentation to verify (i) whether solvates of budesonide do exist and (ii) which solvates, if any, of budesonide may be prepared. In conclusion, the specification, while being enabling for compositions comprising budesonide in the form of a neutral compound and/or pharmaceutically acceptable acid addition

salts thereof, does not reasonably provide enablement for compositions comprising solvates of budesonide.

Claims 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions suitable for the treatment of some respiratory diseases (e.g. asthma), does not reasonably provide enablement for compositions comprising budesonide that are characterized by the property of being suitable for the prevention of any respiratory disease nor for the treatment of all respiratory diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad with regards to the respiratory disease that the claimed composition is recited as being suitable to treat or prevent (i.e. prophylaxis). It is noted that the term "prophylaxes" is not defined in Applicant's specification. Thus, "prophylaxis" is interpreted to mean absolute prevention.

Nature of the invention/State of the Prior Art

The prior art teaches that the conventional treatment of COPD includes the symptomatic treatment by the administration of bronchodilators and anti-inflammatory corticosteroids (e.g. budesonide) (de Boer, W. I. "Potential New Drugs for the Treatment of Chronic Obstructive Pulmonary Disease," *Expert Opin. Investig. Drugs*, **2003,** 12(7), 1067-86, especially at 1067). De Boer teaches that the conventional treatment of COPD by administration of a bronchodilator and/or a corticosteroid fail to prevent the continued decline in lung function and increased airway inflammation over time (*Id.* at 1067). Thus, the administration of budesonide or another anti-inflammatory corticosteroid is not art-recognized as being suitable for the prevention of COPD, prevention of COPD symptoms, etc., and Applicant has not provided data to the contrary. It is also noted that once someone has a COPD, the disease cannot be prevented.

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations

thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970).

Guidance/Working Examples

Applicant provides no data or guidance regarding prevention, aside from indicating that any of the laundry list of drugs identified in the specification may be administered to a patient in need thereof. Because the art recognizes that COPD and/or COPD-induced inflammation cannot be prevented by administration of a corticosteroid (budesonide) and Applicant provides no substantive guidance for prevention of any respiratory disease, let alone COPD, an ordinary skilled artisan would be required to undertake burdensome experimentation to discover which corticosteroid, if any, and at what dosage might be suitable to prevent COPD or prevent COPD symptoms.

In conclusion, , because the specification, while being enabling for compositions suitable for the treatment of some respiratory diseases (e.g. asthma), does not reasonably provide enablement for compositions comprising budesonide that are characterized by the property of being suitable for the prevention of any respiratory disease nor for the treatment of all respiratory diseases

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al. (WO 2003/066031) in view of Uekama et al. ("Cyclodextrin Drug Carrier Systems," *Chem. Rev.* 1998, *98*, pp 2045, 2048 (Table 2); and 2063), wherein US 2005/0085445 is being used as the English language equivalent of WO 2003/066031. All citations to Muller are to the English equivalent US publication.

Applicant Claims

Applicant claims a pharmaceutical composition comprising (i) any HFA (hydrofluoroalkane), (ii) a drug (dependent claim 6 limits the drug to those selected from a Markush group consisting of various drugs, including the elected drug, budesonide, and (iii) a partially or fully acylated alpha-, beta-, or gamma-cyclodextrin.

Claim Interpretation

Regarding claims 8-9, the recited intended use of the claimed composition is not considered to impart any structural component on the claimed composition. Thus, the intended use is given no patentable weight and any reference teaching or suggesting the composition of claim 1 is adequate to meet the limitations of claims 8-9. It is also noted that Applicant's use of comprising language does not exclude formulations comprising additional components.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Muller teaches stabilized pharmaceutical HFA suspension formulations comprising (i) at least one pharmaceutical ingredient (e.g. budesonide), (ii) at least one propellant (e.g. HFA 227 or HFA 134a), (iii) a native or modified alpha-, beta-, or gamma-cyclodextrine (e.g. hydroxypropyl-beta-cyclodextrine), and (iv) at least one hydrophilic additive (e.g. PEG or PVP) (title, abstract; [0014]-[0023]. Muller's preparation of the formulations involves dissolving components (i) and (iii)-(iv) by mixing with ethanol ([0029]). The solution formulation is transferred into a pressure-resistant container fitted with a metering valve and the suspension is formed upon addition to the solution formulation of the HFA propellant ([0029]-[0041]).

Uekama teaches that the most common pharmaceutical application of cyclodextrins is to enhance solubility, stability, and bioavailability of drug molecules, and that natural cyclodextrins generally exhibit poor water solubility (pp 2045). A variety of cyclodextrin derivatives are reported by Uekama and described in pharmaceutical applications, including peracylated cyclodextrins, such as 2,3,6-tris-O-acetylcyclodextrin, 2,3,6-tri-O-hexanoylcyclodextrins, 2,3,6-tri-O-valerylcyclodextrins, etc. (pg. 2047, Table 1; pg. 2048, Table 2, left column). The solubility behavior of various peracetylated-cyclodextr0ins in ethanol/water mixtures from 0%

v/v ethanol to 100% v/v ethanol is depicted in Figure 2 on page 2048. Compared to beta-cyclodextrin all but one of the peracylated cyclodextrins depicted in Figure 2 exhibited greater solubility in 100% ethanol. Uekama also teaches various peracylated cyclodextrins as being suitable to obtain prolonged-release pharmaceutical formulations (pg. 2063, right column).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Muller lacks the teaching of formulations comprising partially or fully acylated cyclodextrins. This deficiency is cured by the teachings of Uekama.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify the teachings of Muller and utilize peracylated cyclodextrins in lieu of or in addition to hydroxy-propyl cyclodextrin, because it is well known in the art to modify the structure of naturally occurring cyclodextrins to obtain cyclodextrin derivatives exhibiting more desirable solubility properties and to stabilize active agents combined with the cyclodextrins. An ordinary skilled artisan would also have been motivated to utilize a peracylated cyclodextrin derivative, such as any one of those taught by Uekama, because these cyclodextrin derivatives can be used to prepare prolonged release drug formulations. It would be desirable to administer a prolonged release drug formulation in the instances, wherein the typical drug dosing regimens requires several daily administrations. A prolonged release dose would require the patient to remember fewer dosing events per day and would reasonably be expected to enhance patient compliance with pharmacotherapy. An

ordinary skilled artisan would have had a reasonable expectation of obtaining HFA/drug/acylated drug formulations, because HFA/drug/hydroxypropyl cyclodextrin/drug formulations are known to be suitable and both hydroxypropyl cyclodextrin and the acylated cyclodextrins tested by Uekama are soluble in ethanol. Regarding claim 3 and the recitation of a solution, although Muller's end formulation is a suspension formulation, it is the Examiner's position that an ordinary skilled artisan would readily expect that solution formulations can be obtained by the addition of more solvent (i.e. ethanol). Therefore, the recitation of a solution formulation is considered to be prima facie obvious. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The following U.S. patent documents are considered relevant, because these teach pharmaceutical formulations comprising acylated cyclodextrins: (a) U.S. Patent No. 6,204,256; (b) U.S. Patent No. 5,91 6,883; (c) U.S. Patent No5,718,905; (d) U.S. Patent No 5,686,487 (treatment of cataracts by application of an aqueous formulation comprising acylated cyclodextrins); (e) U.S. Patent No 5,654,442 (pharmaceutical compositions comprising acylated gamma-cyclodextrins; and (f) U.S. Patent No 5,183,883 (acylated cyclodextrins in admixture with adriamycin).

Claims 1-6 and 8-9 are rejected. Claims 7 and 10 are withdrawn from consideration. The specification and drawings are objected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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